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Concurrent Thrombotic Thrombocytopenic Purpura and Immune Thrombocytopenic Purpura in an HIV-Positive Patient: Case Report and Review of the Literature

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Immune thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP) have each been associated with HIV infection. Sequential occurrence of these two diseases with a disease-free interval has been occasionally reported in the literature, whereas simultaneous manifestations of these two diseases have not been described. Here, we report an AIDS patient who was initially diagnosed as having TTP and showed an apparent partial response to plasmapheresis but was found to have a clinical course similar to ITP. Although precise mechanisms for the development of TTP and ITP in these patients are unclear, we offer several hypotheses. It is important to recognize that these two processes may be seen concurrently. © 1996 Wiley-Liss, Inc.

Key words: HIV, TTP, ITP

INTRODUCTION

Two seemingly different diseases have been observed in HIV-infected patients: immune thrombocytopenic purpura (ITP), with over 700 HIV-positive ITP patients described in the literature [1], and less common but increasingly more frequently found thrombotic thrombocytopenic purpura (TTP), with more than 40 cases having been reported at the time of this review [2–6]. Although both diseases have been reported in the same patient at different times [7–10], concurrent ITP and TTP in the same patient have not been reported before. We report a case of an AIDS patient first diagnosed with TTP, initially partially responding to daily plasmapheresis; however, while the patient was still receiving plasmapheresis, her unremitting thrombocytopenia followed a course that clinically resembled ITP and responded to therapy directed towards this disease process.

CASE REPORT

A 38-year-old Hispanic female, HIV positive since 1990, presented to Harbor-UCLA Medical Center on November 4, 1993, complaining of headache and sore throat of 1-week duration. Prior to admission, she experienced slurred speech as well as left hand cramping, followed by paresthesias of her entire left side. She also had mild left lower extremity and left upper extremity weakness for 1 hr. Her symptoms had resolved at the time of her arrival to the hospital. On the morning of her admission, she had had a generalized tonic-clonic seizure, which lasted approximately 20–30 sec. Her history was significant for recent *Pneumocystis carinii* pneumonia as well as sinusitis and recurrent vaginal infections. She had no history of alcohol, tobacco, or intravenous drug abuse. Her platelet counts had been decreased since January, 1993 (Table I), although there were no signs of bleeding, and all laboratory chemistry test results were within normal limits. Her medications on admission included zidovudine, acyclovir, dapsone, and fluconazole. She was compliant with all medications. Physical examination revealed an afebrile, tachycardiac, normotensive female. Her skin was mildly jaundiced and erythematous. Two hemorrhagic lesions on her palate and ecchymosis and petechiae over right shoulder, both hands, and lower extremities were noted. Her neurologic examination results were within normal limits. The remainder of her physical

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TABLE I. Change in Platelet Count Prior to Admission*

Date	Platelet count ($\times 10^9$/liter)
1/14/93	145
2/18/93	110
3/18/93	102
4/22/93	90
8/26/93	69
10/21/93	37

*During the course, hemoglobins had been stable, bilirubin, blood urea nitrogen (BUN) and LDH were all within normal limits. No fragmented red cells were observed on 4/22/93, 8/26/93, or 10/21/93 on the peripheral blood smear.

examination was unremarkable. A computed tomogram of her head was negative. Laboratory values included a hematocrit of 0.132 liter/liter (normal 0.350–0.440), hemoglobin of 44 g/liter (normal 117–149), and a white blood cell count of 3.6 × 10^9/liter (normal 4.0–8.4), with a 100 cell differential of 56% neutrophils, 26% lymphocytes, and 18% monocytes. The platelet count was 7.0 × 10^9/liter (normal 153–403). Coagulation study results were within normal limits except for fibrin split products which were >40 μg/ml (normal <10). The reticulocyte count was 6.8%. The total bilirubin was 2.5 mg/dl (normal 0.2–1.2), with a direct bilirubin of 1.2 mg/dl (normal <0.2). The direct Coomb's test was negative. Her blood urea nitrogen was 23.0 mg/dl (normal 10–20), lactic acid dehydrogenase (LDH) 778 U/liter (normal 109–230), asparate aminotransferase 97 U/liter (normal 3–40), and alanine aminotransferase 65 U/liter (normal 3–45). Serum creatinine, amylase, alkaline phosphatase, and α-glutamyl transpeptidase were all within normal limits. The peripheral smear revealed moderate numbers of fragmented red cells, with increased polychromasia and decreased platelets. Examination of the bone marrow biopsy revealed a hypocellular bone marrow with relative erythroid and megakaryocytic hyperplasia and one platelet thrombus in a small blood vessel. The results were consistent with TTP.

The patient was initially treated with 5 units of packed red blood cells and 6 units of fresh frozen plasma. Phenytoin (Dilantin) was given to prevent further seizures. Zidovudine was discontinued; however, the patient remained on all other previous medications. Therapeutic plasma exchange using fresh frozen plasma was initiated, and the patient's platelet count rose to 21 × 10^9/liter. Her daily platelet counts and modes of treatment are illustrated in Figure 1. The patient had symptomatically improved, with no further neurological problems, a normal LDH, and a stable hematocrit. Plasmapheresis was discontinued on day 4 but was resumed the following day and afterwards. In spite of the initial response to treatment, the platelet count did not rebound after daily plasmapheresis. The patient became febrile on the ninth hospital day. There was bleeding from the Quinton catheter and blood culture grew *Staphylococcus aureus* on day 10. Vancomycin, gentamicin, and mezlocillin were given. Gentamicin and mezlocillin were discontinued 4 days later, but the patient was maintained on vancomycin until discharge. Daily plasma exchange was replaced by daily infusion of large volumes of fresh frozen plasma because of wound infection. No fragmented red cells were seen on the peripheral blood smear. By hospital day 13, the platelet count was 13 × 10^9/liter in spite of the facts that the patient was afebrile and the infection was totally under control. It was thought that, given the fact that the patient's platelet count prior to admission had been steadily decreasing, the current thrombocytopenia was secondary to at least two processes: HIV-related chronic ITP as well as TTP. Gammaglobulin infusion, zidovudine and solumedrol were employed. The platelet count increased over the next 9 days to 134 × 10^9/liter.

The patient was discharged on December 1, 1993. She remained on oral prednisone (20 mg QD), which was tapered slowly on an outpatient basis. Meanwhile, the patient was placed on oxacillin. No recurrence of TTP or ITP was noted. The patient died on August 25, 1994, 10 months after initial diagnosis of TTP, from respiratory failure secondary to disseminated Kaposi's sarcoma. Permission for autopsy was not granted.

SUMMARY OF DATA FROM THE LITERATURE

Five additional cases of HIV-associated TTP and ITP have been reported in the literature (Tables II and III) [7–10]. Four of these patients had a history of ITP, occurring 10 months, 32 months, 11 years, and 6 weeks prior to the presentation of TTP (Table III). The fifth patient developed transient ITP 5 months after the recovery from TTP. All patients were males, with a mean age of 33 years and a median age of 34 years. Two of them were HIV clinical stage II, being only serologically positive for HIV; the other three patients had AIDS, with one of them having Kaposi's sarcoma and the other two having recurrent or life-threatening opportunistic infections. All these patients received fresh frozen plasma infusion or plasma exchange. Some of them were also treated with steroids, gammaglobulin, and vincristine. All of them achieved partial or complete remissions from TTP. However, one of the patients died of pulmonary embolism 2 weeks later, and another patient died of a relapse of TTP, refractory to therapy.

In contrast to the cases with HIV-associated TTP and ITP, three of the five non-HIV-associated TTP and ITP patients were females [11–13]. Their mean age was 23 years, with a median age of 22 years. Two patients had chronic ITP prior to the development of TTP; the other three patients developed ITP 12 weeks, 13 months, and 5 months after the episodes of TTP. Both patients with

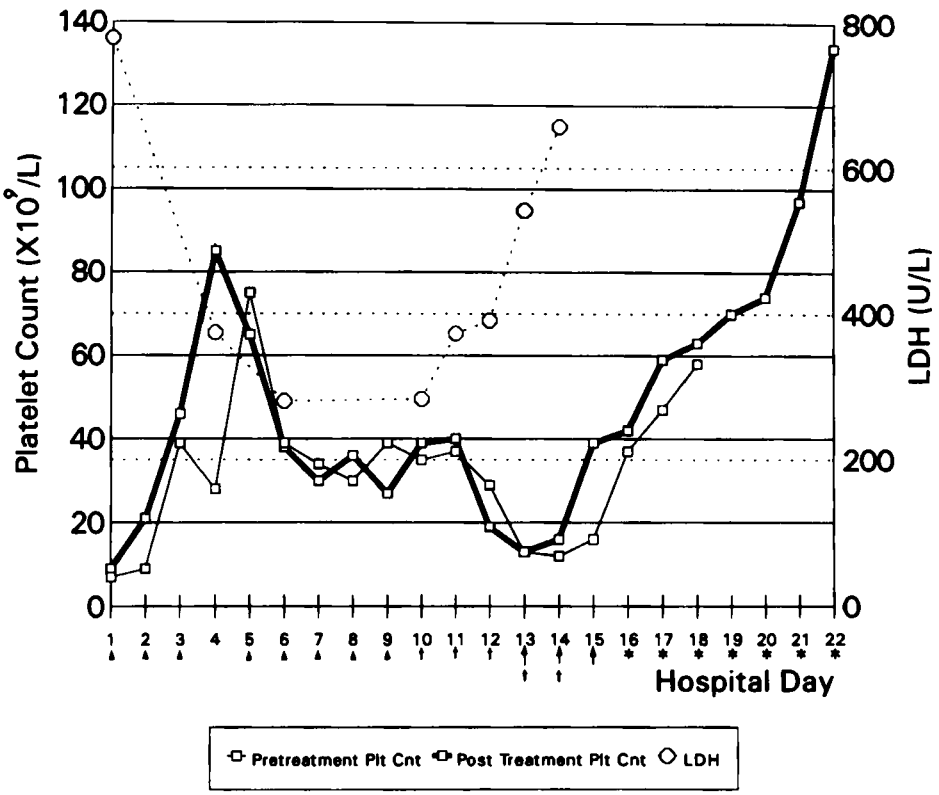

Fig. 1. Graph illustrating the daily changes of platelet counts and fluctuations of lactic acid dehydrogenase (LDH) in response to treatment during the hospital course. Arrowheads, plasmapheresis; daggers, FFP infusion; arrows, IV IgG; asterisks, steroids.

TABLE II. Summary of Clinical Information at Presentation for TTP in HIV-Infected Patients With Associated ITP*

References	Age (years)	Sex	Fever	Neurological disease	Plts (×10⁹/liter)	LDH (U/liter)	BUN (mg/dl)	Creatine (mg/dl)	Peripheral smear
Meisenberg et al., 1988 [7]	25	M	No	No	10	945	48	2.4	MAHA
Routy et al., 1991 [8]	35	M	Yes	Yes	40	470	112.3	5.7	MAHA
Routy et al., 1991 [8]	31	M	Yes	Yes	15	27.5	20.7	1.9	MAHA
Shivaram and Cash, 1992 [9]	34	M	Yes	Yes	10	ns	55	1.6	MAHA
Manner et al., 1993 [10]	42	M	Yes	Yes	Decreased	ns	ns	ns	ns
Present study	38	F	No	Yes	7	778	23	0.8	MAHA

*ns, not stated; MAHA, microangiopathic hemolytic anemia.

TABLE III. Summary of Modes of Treatment and Clinical Course of HIV-Infected Patients With TTP and ITP*

References	HIV stage	Therapy	Outcome	Onset of ITP
Meisenberg et al., 1988 [7]	HIV⁺ only	P	Complete remission	5 Months after TTP
Routy et al., 1991 [8]	HIV⁺, Kaposi's sarcoma	St, Sp, P, FFP	Dead of disease, hospital day 6	10 Months prior to TTP
Routy et al., 1991 [8]	HIV⁺	P, V, St	Complete remission	32 Months prior to TTP
Shivaram and Cash, 1992 [9]	AIDS	FFP, P	Complete remission	11 Years prior to TTP
Manner et al., 1993 [10]	AIDS	P, St, IgG, V, FFP	Complete remission, died 2 weeks later of PE	6 Weeks prior to TTP
Present study	AIDS, PCP	P, FFP, IgG, St	Complete remission, dead of other causes (9 months later)	Concurrent TTP/ITP

*P, plasmapheresis; FFP, fresh frozen plasma infusion; St, steroids; V, vincristine; Sp, splenectomy; IgG, intravenous IgG; PE, pulmonary embolus.

chronic ITP were treated with splenectomy. It appears that splenectomy did not deter the occurrence of TTP.

DISCUSSION

Since the initial description by Moschcowitz in 1924 [14] of a 16-year-old girl who died of TTP, the condition has been recognized as an uncommon but often life-threatening syndrome characterized by the pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), neurologic abnormalities, fever, and renal dysfunction. It occurs more frequently in women than in men, usually in the third decade of life [15]. Recurrent attacks of TTP are reported in approximately 7.5% of cases [15]. Familial and congenital variants have also been described [16]. The clinical manifestations of TTP are the consequence of arteriolar and/or capillary platelet thrombi, which involve multiple organs and systems without surrounding inflammatory reaction. Coagulopathy other than mild elevation of fibrin split products secondary to intravascular thrombi is uncommon. The etiology and pathogenesis are not fully understood, although multiple factors, such as drugs, infectious agents including HIV-1, pregnancy, immune disorders (systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, Grave's disease, and others), and underlying malignancy, have been considered to precipitate the illness. Because most patients with TTP presented with MAHA, thrombocytopenic purpura, and neurologic symptoms and because hemolytic uremic syndrome (HUS) is characterized by a triad of thrombocytopenia, MAHA, and acute renal failure in children, a unified concept to include these two diseases by using the term thrombotic microangiopathy (TMA) has been suggested recently [3,4,17].

Several hypotheses have been proposed for the pathogenetic mechanism for TTP, such as 1) endothelial cell injury, 2) presence of a platelet agglutinating factor and/or platelet agglutinating protein with a molecular weight of 37,000 (p37), 3) consumption of abnormally large von Willebrand factor (vWF) or large vWF multimers during acute episodes of TTP, 4) existence of immune complexes or platelet-associated immunoglobulins, 5) alteration of components involving the fibrinolytic pathway, 6) deficiency of prostacyclin (PGI_2) activity that enhances the propagation of platelet aggregation, 7) decreased protein S, and 8) genetic predisposition [18–20]. The primary event in TTP is probably endothelial damage, with secondary platelet adhesion and aggregation leading to intravascular thrombus formation.

ITP is an autoimmune disorder characterized by thrombocytopenia, an essentially normal bone marrow with normal or increased megakaryopoiesis, and absence of intravascular coagulation. The pathogenesis is from circulating immune complexes that attach to platelets, leading to destruction by the reticuloendothelial cells in the spleen, bone marrow, and liver. Immune complex attachment to the megakaryocyte also leads to ineffective platelet production [21].

Patients with HIV-associated ITP have been found to have nearly four fold higher levels of platelet-associated IgG and four fold higher levels of platelet-associated complement than patients with non-HIV-related ITP [22]. Antibody to the 25 kd platelet antigen has been found in HIV-infected patients with or without thrombocytopenia [22]. Louache and associates [23] demonstrated HIV transcripts in megakaryocytes from HIV-positive patients. Dyspoietic features affecting hematopoietic precursors are common in HIV patients [24]. It is possible that platelet glycoproteins are either damaged or altered by direct viral injury or through immune responses to the virus. These factors result in the removal of abnormal platelets from the circulation by the reticuloendothelial system, especially the spleen.

In humans, HIV infects endothelial cells and monocytes-macrophages, among other cells, in addition to CD4 cells. HIV DNA has been demonstrated in the endothelial cells [25]. Indeed, vascular endothelial cell immune function in HIV-infected individuals is impaired, as was demonstrated by Teitel and associates [26]. In their experiments, HIV-exposed endothelial cells were consistently defective in promoting interleukin-2 (IL-2) secretion by CD4 cells. Endothelial cell production of coagulation and fibrinolysis factors has also been shown to be altered, as illustrated by statistically significantly decreased levels in total and free protein S, increased plasminogen activator inhibitor, and increased production of von Willebrand factor [27,28]. Most patients with HIV-1 have markedly elevated antiplatelet IgG, C3, C4, and IgM and elevated circulating immune complexes [29]. The patient described herein had hypergammaglobulinemia, with chronically elevated IgG levels ranging between 2,000 and 3,500 mg/dl (normal 564–1785) and consistently elevated IgM levels in the 300–400 mg/dl (normal 63–277) range.

The therapeutic strategies for HIV-associated ITP are 1) careful follow-up or AZT (Zidovudine) if the platelet count is greater than 20×10^9/liter, with no bleeding, and 2) low-dose steroids or AZT if the platelet count is less than 20×10^9/liter or if there is bleeding. Should the patient be unresponsive, splenectomy should be performed. The third line of treatment includes high-dose immunoglobulin, anti-Rh immunoglobulin, cytotoxic drugs, and Danazol [22]. On the other hand, the treatment of choice for TTP is fresh frozen plasma infusion and plasma exchange. Antiplatelet agents may be given, especially for maintenance therapy. Steroids, vincristine, and splenectomy may be considered if the patient does not respond to the above-described regimen.

Our case and those cases reported in the literature illustrate that TTP is a treatable disease, which often

responds to plasma exchange with or without antiplatelet agents, steroids, and vincristine. The association of TTP and ITP in the same patient supports the notion that TTP and ITP share similar pathogenetic mechanism. It is interesting to note that ITP usually occurs prior to TTP. This may be due to the facts that 1) ITP is more common than TTP and 2) patients with ITP are immunologically aberrant and are predisposed to TTP. The older age group and a predominantly male population in HIV-associated TTP and ITP in comparison to non-HIV-infected patients reflect the uniqueness of that patient population. As yet the data are insufficient to determine whether HIV-infected patients with TTP respond to therapy comparably to non-HIV-infected patients.

CONCLUSIONS

TTP is a syndrome with diverse etiologies and is probably mediated by a variety of pathogenetic mechanisms. The central problem in HIV-infected patients is immune dysfunction and immune deficiency due to the fact that HIV attacks and kills CD4 cells and produces latent infection of monocytes-macrophages. Patients with HIV infection also have a polyclonal B-cell activation resulting in hyperglobulinemia and the formation of antibodies. Distortion of the immune system by HIV may explain the reason why ITP is frequently seen in HIV-infected patients. One may further speculate that alternate episodes of TTP and ITP, the occurrence of chronic ITP or chronic TTP, and relapsing ITP or TTP indicate that dysfunction of the immune system along with other factors plays a role in the initiation and the development of these diseases. Review of our case and the cases previously reported suggests that patients with HIV may be at greater risk of developing TTP. Because of the treatment differences for these two diseases, physicians who tend HIV-infected patients should be aware of the association so that prompt and specific treatment may be instituted.

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